



Strategies for Improving Drug Interaction Alerts for Clinical Decision Support (CDS)

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FDA Advisory Committee Meeting, September 25, 2013

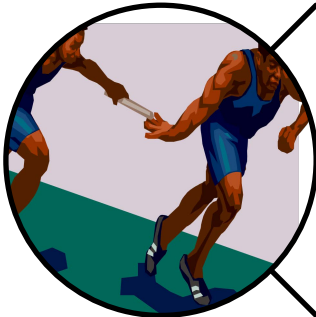
FDB (First Databank)

- FDB is a subsidiary of Hearst Corporation and the leading provider of drug knowledge that helps healthcare professionals make precise medication-related decisions.
- FDB creates and maintains widely used drug knowledge, software for drug knowledge integration, and drug reference products. The firm has partnered with other information system developers to make drug information useful within the workflow for a wide range of healthcare professionals.
- FDB's drug knowledge supports pharmacy dispensing, formulary management, drug pricing analysis, medical insurance claims processing, computerized prescriber order entry (CPOE), electronic health/medical records (EHR/EMR), electronic prescribing, and electronic medication administration records (EMAR) systems.
- FDB influences the incidence of medication errors and adverse events associated with prescription drugs that have an impact on healthcare costs and the overall quality of patient care.

AGENDA



Medication CDS lives in a complicated realm, but editorial policies supporting evidence-based content is a focus for FDB



Three pronged approach to alert fatigue has FDB moving the mark clinically



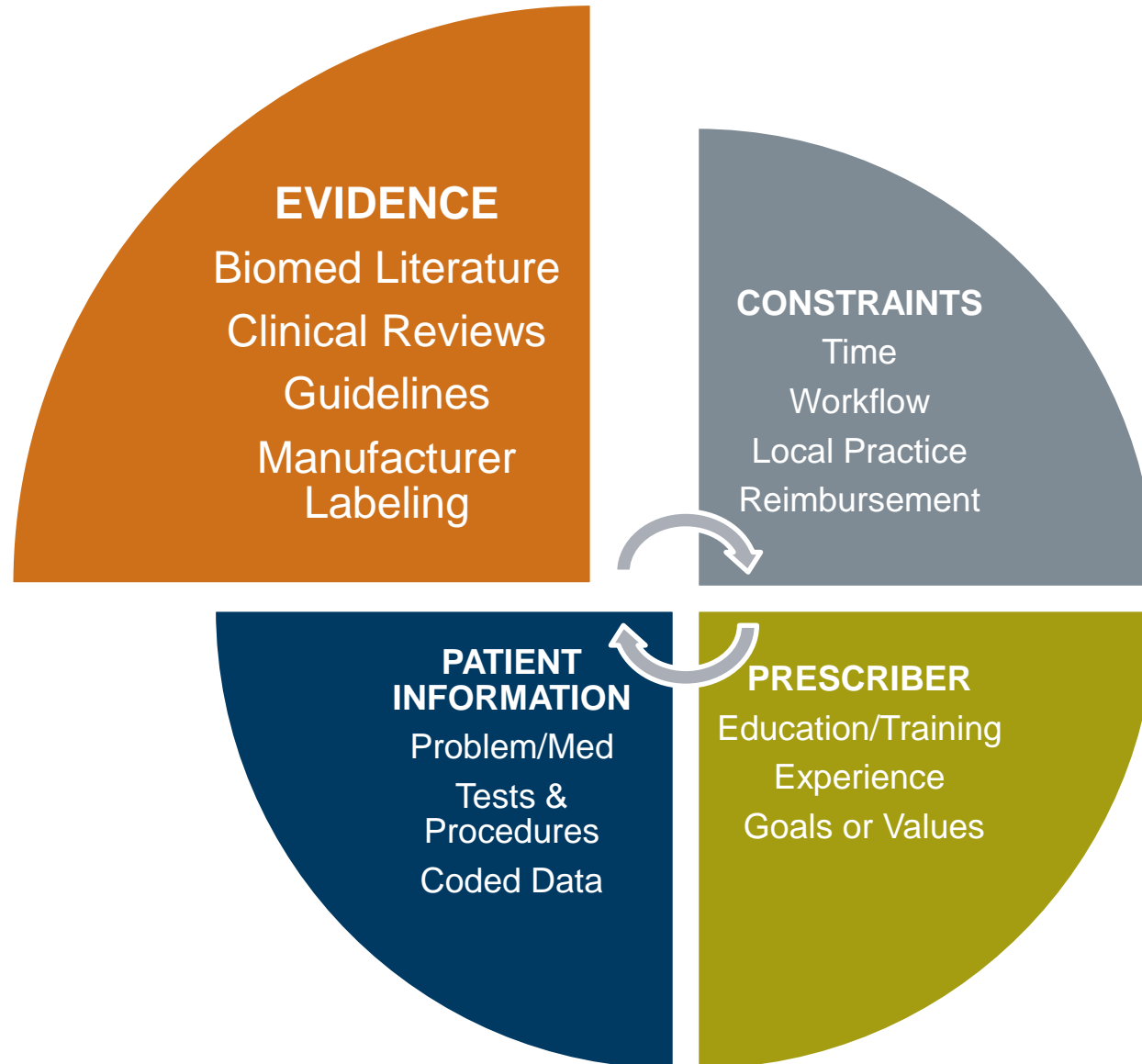
Content with additional drug or patient parameters and filters including med cycle focus

FDB FOUNDATIONAL APPROACH

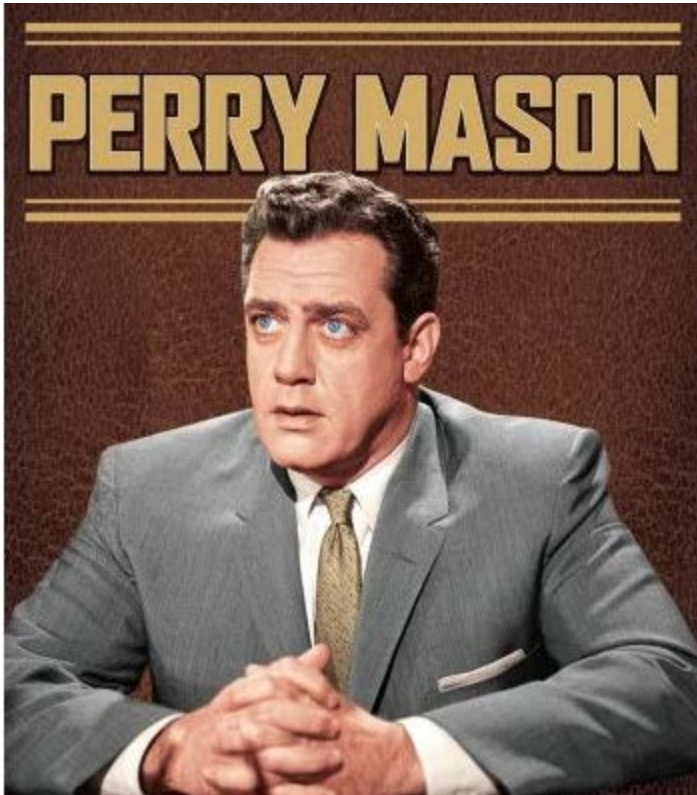
Surveillance for Evidence

CDS Lives in this Realm

A Multitude of Changing Factors in Clinical Decision Making



EVIDENCE is in the Eye of the Beholder!



- *Content creation responsibilities*
 - Experienced Clinical Pharmacists with honed judgment, expert review prn
 - Understanding of health system applications and workflow
- *Capture drug information*
 - “trigger events” – tracking systems
 - Accountable assessment plan
- *Comprehensive evidence review*
 - timely review enforced
 - compliance with Editorial Policies
 - consistent with quality controls
 - new knowledge sources acquired (drug metabolism literature database)

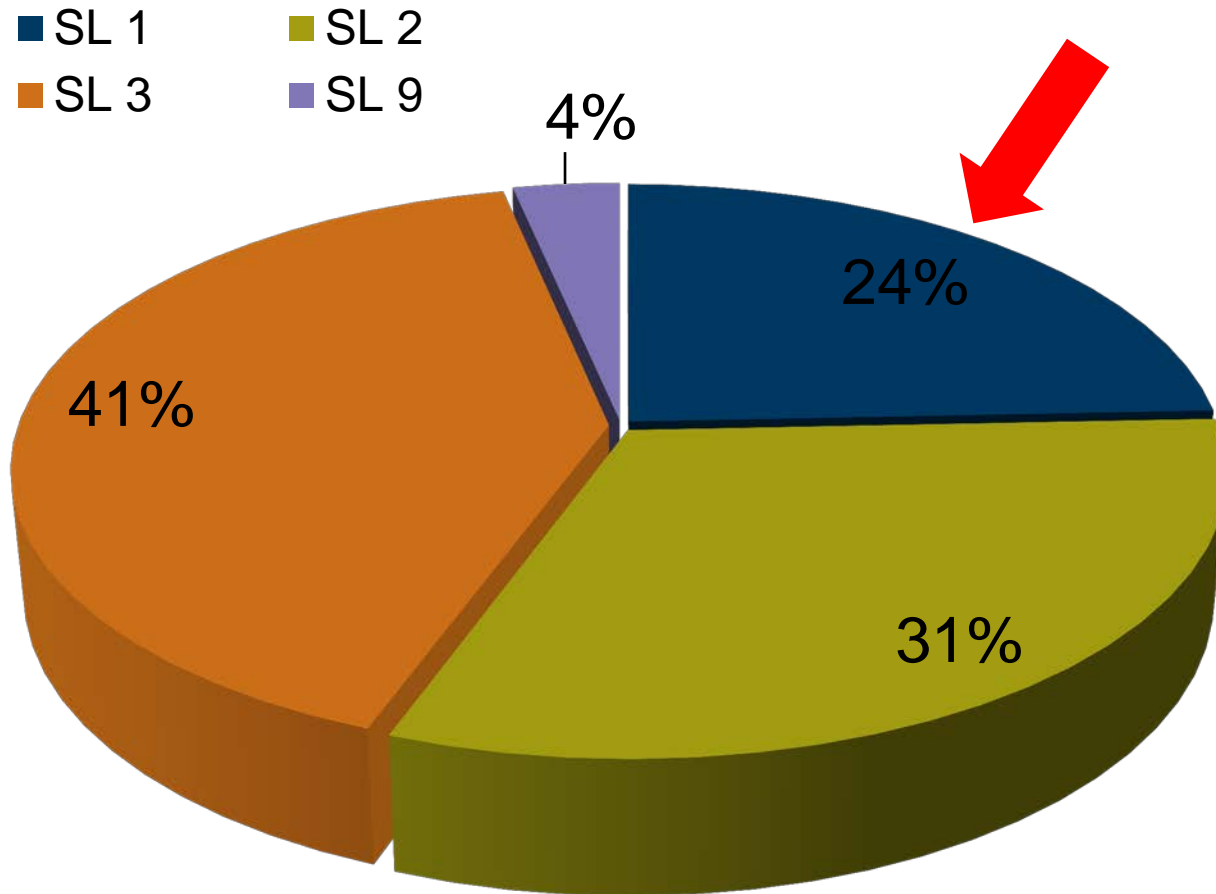


Evaluations of Drug Interactions (EDI)

- Loose-leaf reference started in 1984, bimonthly updates
- 18 chapters, 2000 pages, based on major therapeutic classes
- 14 member external advisory board
- Sections: Title of DDI, summary, related drugs, mechanism, recommendations, references, tables



FDB DDI Severity Level Breakdown, N ~ 1600



Alert Fatigue or Knowledge Denial?

New antiepileptic drug safety information is not transmitted systematically and accepted by U.S. neurologists ☆

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Highlights

- Survey US **neurologists' knowledge of FDA safety warnings for AEDs.**
- Respondents received safety information non-systematically from multiple sources.
- One-fifth **(20%) did not recognize recently identified, serious AED safety risks** (e.g., suicidality, birth defects, side effects).
- FDA-recommended pharmacogenomic screening for carbamazepine was not carried out.
- Neurologists would prefer receiving FDA safety updates via specialty organizations.

Pace of “official” Change Notice

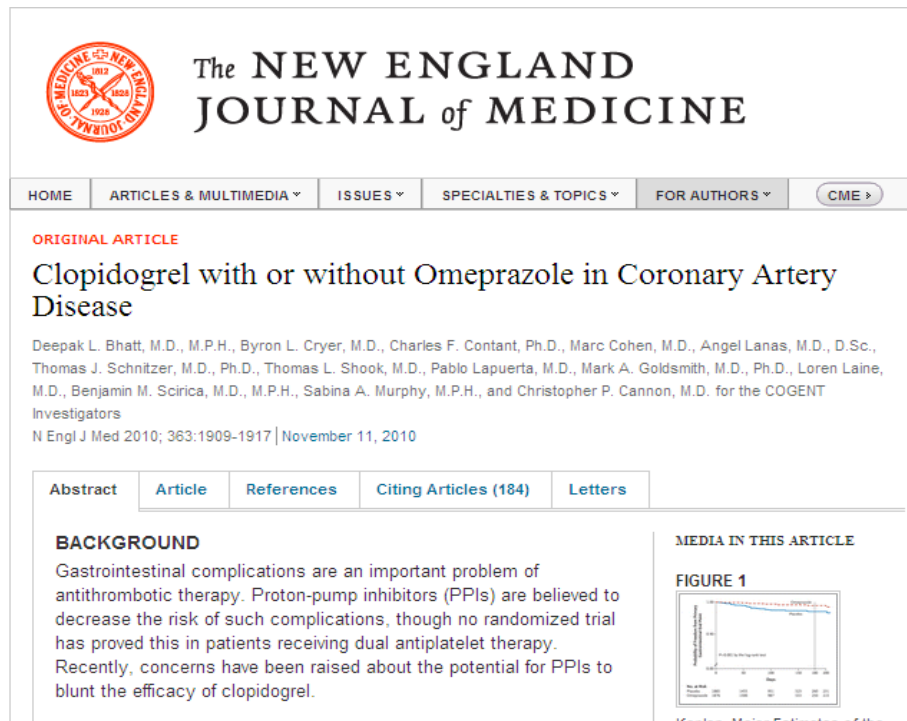
Year	FDA MedWatch Alerts	Drug Safety Withdrawals
2009	122	0
2010	140	0
2011	136	1
2012	169	3
2013 (YTD)	138	1

Making Headway with Alert Management



Drug-Drug Interactions: FDB Making Hard Choices

- Over 75 drug interaction pairs are **strength-breakouts**
- Drug interaction applications can take advantage of **route breakouts** (e.g., topicals)
- **Limiting class effects** - clopidogrel/proton pump inhibitors
 - esomeprazole (Nexium) & omeprazole (Prilosec), Severity Level=2
 - lansoprazole (Prevacid), pantoprazole (Protonix) changed to Severity Level=3



The screenshot shows the article page for "Clopidogrel with or without Omeprazole in Coronary Artery Disease" from The New England Journal of Medicine. The page includes the journal's logo, navigation tabs (HOME, ARTICLES & MULTIMEDIA, ISSUES, SPECIALTIES & TOPICS, FOR AUTHORS, CME), and the article title. Below the title is the author list: Deepak L. Bhatt, M.D., M.P.H., Byron L. Cryer, M.D., Charles F. Contant, Ph.D., Marc Cohen, M.D., Angel Lanas, M.D., D.Sc., Thomas J. Schnitzer, M.D., Ph.D., Thomas L. Shook, M.D., Pablo Lapuerta, M.D., Mark A. Goldsmith, M.D., Ph.D., Loren Laine, M.D., Benjamin M. Scirica, M.D., M.P.H., Sabina A. Murphy, M.P.H., and Christopher P. Cannon, M.D. for the COGENT Investigators. The publication date is November 11, 2010. The article is categorized as an "ORIGINAL ARTICLE". Below the article title, there are tabs for "Abstract", "Article", "References", "Citing Articles (184)", and "Letters". The "BACKGROUND" section is visible, discussing gastrointestinal complications and the use of proton-pump inhibitors (PPIs) in patients receiving dual antiplatelet therapy. A "MEDIA IN THIS ARTICLE" section is also present, featuring "FIGURE 1" which is a Kaplan-Meier plot showing the estimated cumulative incidence of major adverse cardiovascular events (MACE) over time for two groups: "PPIs" (blue line) and "No PPIs" (red line). The plot shows that the PPI group has a lower cumulative incidence of MACE compared to the No PPI group.

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Clopidogrel with or without Omeprazole in Coronary Artery Disease

Deepak L. Bhatt, M.D., M.P.H., Byron L. Cryer, M.D., Charles F. Contant, Ph.D., Marc Cohen, M.D., Angel Lanas, M.D., D.Sc., Thomas J. Schnitzer, M.D., Ph.D., Thomas L. Shook, M.D., Pablo Lapuerta, M.D., Mark A. Goldsmith, M.D., Ph.D., Loren Laine, M.D., Benjamin M. Scirica, M.D., M.P.H., Sabina A. Murphy, M.P.H., and Christopher P. Cannon, M.D. for the COGENT Investigators

N Engl J Med 2010; 363:1909-1917 | November 11, 2010

Abstract Article References Citing Articles (184) Letters

BACKGROUND

Gastrointestinal complications are an important problem of antithrombotic therapy. Proton-pump inhibitors (PPIs) are believed to decrease the risk of such complications, though no randomized trial has proved this in patients receiving dual antiplatelet therapy. Recently, concerns have been raised about the potential for PPIs to blunt the efficacy of clopidogrel.

MEDIA IN THIS ARTICLE

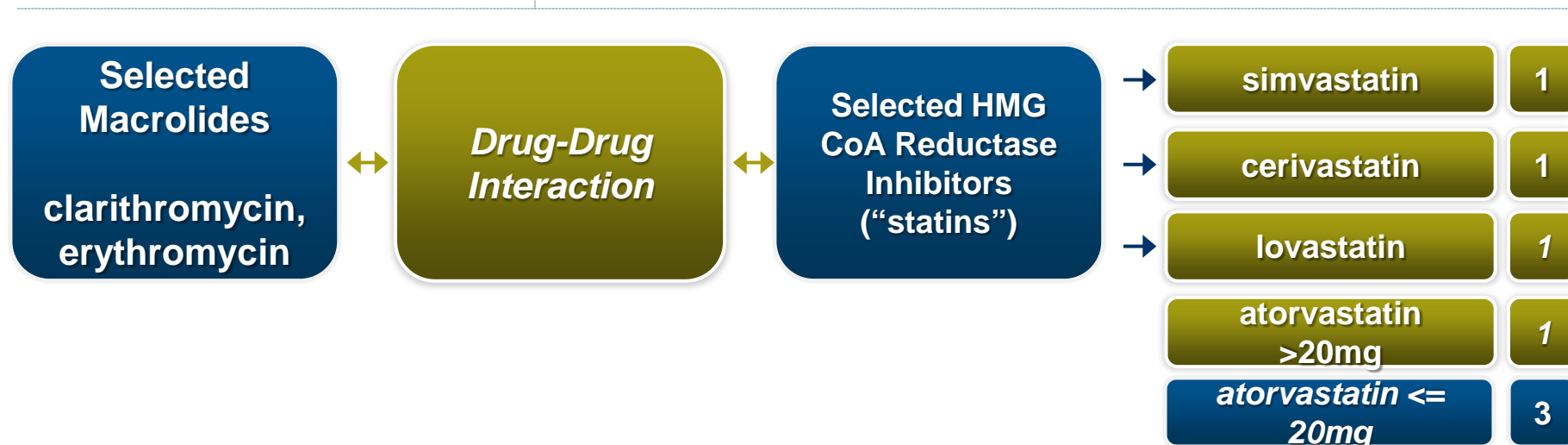
FIGURE 1



Kaplan-Meier Estimates of the

Fine-Tuned Content: Drug-Drug Interactions

Breakout Ingredients & Adjusting Severity Level based on agent-level evidence



Bottom Line: Fewer Inappropriate Alerts

FDB's AlertSpace™

Allowing for Local Customization

Implementation of Authoritative DDI Subsets

DRUG-DRUG INTERACTIONS

Dashboard | Work List | Pending Publish | Published | Publish History

Interaction Name **Search**

[Hide Filter](#) | [Clear Filter](#)

Alert Status:

☒ Show All

☐ On ☐ Off

Severity:

☐ 1 - Contraindicated

☐ 2 - Severe

☐ 3 - Moderate

☐ 9 - Undetermined

☐ Custom - Severity

FDB Updates:

☐ New Interactions

☐ Removed Interactions

☐ Severity

☐ Monograph

☐ Clinical Effect Codes

☐ Reference Categories

☐ Clinical Formulations

Since:

☒ ☐ Specific Date

My Updates:

☐ Severity

☐ Clinical Formulations

☐ Interaction Turned Off

Reference Categories:

☐ Manufacturer Information

☐ Human Clinical Trial

☐ Case Report

☐ Meeting Abstract

☐ In Vitro Animal Study

☐ Review

Clinical Effects:

☐ Avoid concurrent use when possible

☐ Conflicting evidence exists in medical literature

☐ Contraindicated in some patients

☐ Labeling conflicts between countries or products

ONC Status:

☒ High Priority

☐ Low Priority

☐ Not on ONC list

Apply Filter

Drug-Drug Interactions: 41 results

[Export](#) [Print](#) [Help](#)

Set All: ☒ On ☐ Off **Apply** Sort By Per Page - 20 Page 1 of 3

Drug-Drug Interactions			Severity Level			Clinical Formulations		Monograph		
Status	Description	ONC Status	Published	Direction	Previous	FDB Updates	Year Edits	FDB Updates	FDB Updates	Mono Code
On	Atazanavir; Nelfinavir/Proton Pump Inhibitors	High	1 - Contraindicated							1287
On	Atomoxetine; Reboxetine/Monoamine Oxidase Inh...	High	1 - Contraindicated							1228
On	Azathioprine; Mercaptopurine/Feboxostat	High	1 - Contraindicated							1837
On	Bosentan/Protease Inhibitors	High	2 - Severe							1905
On	Ergotamine Derivatives/Itraconazole; Ketoconazole	High	1 - Contraindicated							1221
On	Ergotamine Derivatives/Selected Macrolide Antib...	High	1 - Contraindicated							336
On	Ergotamine Derivatives/Selected Potent CYP3A4 I...	High	1 - Contraindicated							2283
On	Fentanyl/MAOIs	High	1 - Contraindicated							1480
On	Irinotecan/Atazanavir	High	1 - Contraindicated							1286
On	Irinotecan/Ketoconazole	High	1 - Contraindicated							1208
On	Lovastatin (> 20 mg); Simvastatin (> 10 mg)/Verap...	High	1 - Contraindicated							2022

CUSTOM SEVERITY LEVEL- Targeted Alerts

Interaction Details
Alteplase
Anticoagulants
Audit Trail

Alteplase / Anticoagulants

Severity Level:
2-Severe Interaction
Action is required to reduce the risk of severe adverse interaction.

Clinical Effects:
Contraindicated in some patients

Reference Categories:

Manufacturer Information
Human Clinical Trial

Interaction Monograph

Monograph Title
Alteplase/Anticoagulants

Mechanism of Action
The concurrent use of alteplase and anticoagulants may increase the risk of bleeding.(1)

Alert Status:
On
On

Proposed Severity Level:
5
Custom
Apply

First Databank Severity Level:
2 -Severe
Modified by:

References

1. Activase (alteplase, recombinant) US prescribing information. Genentech, Inc. April, 1999.

2. Prabhakaran S, Rivolta J, Vieira JR, Rincon F, Stillman J, Marshall RS, Chong JY. Symptomatic Intracerebral Hemorrhage Among Eligible Warfarin-Treated Patients Receiving Intravenous Tissue Plasminogen Activator for

Crowd Source- Potential Top Customizations

fdb
First Databank

AS-Account39 AS-Contact39 Sign Out

Modules Publish History Top 10 Edits

TOP 10 EDITS

Welcome to AlertSpace Top 10 Edits.
This view shows you how other AlertSpace customers are customizing their alerts. It shows the top ten customizations customers have made per module.

Drug Drug Interactions	Duplicate Therapy	Allergy Picklist	Drug Allergy Allergen Group	Drug Allergy Excipient Ingredient	Drug Disease
*Count indicates number of customers who have made this customization					
2	ACE INHIBITORS/HIGH-DOSE ASPIRIN				
1	ABCIXIMAB/ANTICOAGULANTS				
1	ACE INHIBITORS; ARBS/LITHIUM				
1	5HT-1D AGONISTS/ERGOTAMINES; METHYSERGIDE				
1	ANTICOAGULANTS/SELECTED CEPHALOSPORINS, INJECTABLE				
1	5HT-1D AGONISTS/SSRIS; SNRIS				

NEW FDB CAPABILITY

Customer Alert Reports Feedback Loop



Essential Alert Report Feedback Loop to Prioritize Evidence Review

Count	Status					
Type	Overridden	Filtered	Viewed	Removed	(blank)	Grand Total
<input checked="" type="checkbox"/> Drug-Drug	94	253	0	0	0	347
Contraindicated Drug Combination	1	0	0	0	0	1
Severe Interaction	93	1	0	0	0	94
Moderate Interaction	0	252	0	0	0	252
<input checked="" type="checkbox"/> Drug-Allergy (Active and Inactive Ingredients)	38	0	4	0	0	42
DRUG CLASS MATCH	17	0	3	0	0	20
EXACT INGREDIENT MATCH	3	0	0	0	0	3
BASE INGREDIENT MATCH	1	0	1	0	0	2
CROSS-SENSITIVE CLASS MATCH	2	0	0	0	0	2
Unknown	15	0	0	0	0	15
<input checked="" type="checkbox"/> Drug-Food	0	0	0	0	0	0
<input checked="" type="checkbox"/> Duplicate Therapy	228	0	0	2	0	230
(N/A)	228	0	0	2	0	230
<input checked="" type="checkbox"/> Dose	48	13	0	1	0	62
(N/A)	48	13	0	1	0	62
<input checked="" type="checkbox"/> IV Compatibility	0	0	0	0	0	0
<input checked="" type="checkbox"/> Drug-Disease	658	522	57	8	0	1245
Absolute contraindication	171	0	5	3	0	179
Relative Contraindication	487	0	40	4	0	531
Patient monitoring warning	0	522	12	1	0	535

Creating Additional Parameters for DDI

- Patient
 - New exposure (vs. continued therapy)
 - Normal lab parameters (e.g., K+, INR)
 - # MDs ordering meds
 - Service location (e.g., clinic vs. ICU)
 - Co-morbidities (e.g., renal/hepatic deficits)
 - Pharmacogenomics (slow/fast metabolizers)
- Physician
 - Specialty (e.g., anesthesiology vs. family medicine)
 - Role (e.g., hospitalist vs. intern)
- Drug
 - Probability (rare vs. common) → % occurrence
 - Severity (mild thru severe) → o, /, x (use of standard symbols?)



Implementation for DDI screening Factors

- Who is looking and or acting on alerts?
 - Prescribing vs. dispensing vs. administering
- What other background CDS (implemented)
 - Duplicate therapy
 - Side effects
 - Drug-disease contraindications/precautions
- The user interface (design)
 - Recall and ignore (i.e., I already approved this combo)
 - Symbolic coding (e.g., green, yellow, red or icons)
 - Bundled or prioritized alerts (vs. long list strings)
 - Screen size viewing (32" vs mobile)
 - Audio alerts? Offering alternatives? Ordering labs/monitoring?



PI Issues for Drug Interactions

- Labeling mismatches between 2 drugs
- Label inconsistencies
- Imprecise label narrative
- Outdated labels
- Broad class effect statements

Label Inconsistencies Ex. - Xenazine (9/12)

- The **Highlights section** states “QTc prolongation. **Do not prescribe** in combination with other drugs that prolong QTc. (5.11, 7.5, 7.6, 12.2).”
- **Section 5.11** states “The use of XENAZINE **should be avoided in combination** with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval [see *Drug Interactions (7.5, 7.6) and Use in Specific Populations (8.9)*].”
- **Section 7.5** states “Since XENAZINE **causes a small increase in QTc prolongation** (about 8 msec), the concomitant use with other drugs that are known to cause QTc prolongation should be avoided including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval.”
- **Section 7.6** states “Adverse reactions associated with XENAZINE, such as QTc prolongation, NMS, and extrapyramidal disorders, **may be exaggerated by concomitant use** of dopamine antagonists, including antipsychotics (e.g., chlorpromazine, haloperidol, olanzapine, risperidone, thioridazine, ziprasidone) [see *Warnings and Precautions (5.5, 5.9, 5.11, 5.12) and Drug Interactions (7.5)*].”

[Start Over](#)
[Back to Details](#)

Label and Approval History

Drug Name(s) XENAZINE
 FDA Application No. (NDA) 021894
 Active Ingredient(s) TETRABENAZINE
 Company VALEANT BERMUDA

[Go to Approval History](#)

Label Information

[What information does a label include?](#)

Note: Not all labels are available in electronic format from FDA.

The latest approved label (approved 08/02/2013) is *not available* on this site for XENAZINE, NDA no. 021894

[View the label approved on 07/06/2011 \(PDF\)](#)

To see if other previously-approved labels are available on this site, go to the "[Approval History](#)" section of this page.

Older labels are for historical information only and should not be used for clinical purposes.

Approval History


NDA 021894

Note: Not all reviews are available in electronic format from FDA.

Older labels are for historical information only, and should not be used for clinical purposes.

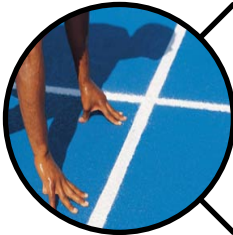
Approval dates can only be verified from 1984 to the present.

Click on a column header to re-sort the table:

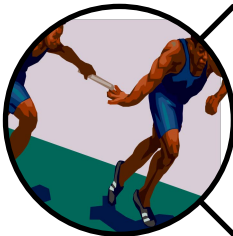
 [Download data](#)

Action Date	Supplement Number	Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
08/02/2013	009	Labeling Revision	Letter (PDF)	Label is not available on this site.
08/17/2012	007	Labeling Revision	Letter (PDF)	Label is not available on this site.
07/06/2011	004	Labeling Revision	Label (PDF) Letter (PDF)	
05/04/2011	005	Labeling Revision	Label (PDF) Letter (PDF)	
12/01/2009	002	Labeling Revision	Letter (PDF)	Label is not available on this site.

Summary



Medication Alerts live in a complicated realm, but evidence-based content is a focus for FDB



FDB's three pronged approach to alert fatigue has evolved, and continues to push the mark clinically



Evolving evidence review sources and strategies needed, along with new module tools/tactics



THANK YOU – Questions?